REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 1-5 and 7-14 are pending in this application. Claims 8 and 9 have been amended to delete the term R_3 = C_1C_6 alkoxy groups. Claims 11, 13, and 14 have been allowed.

In the outstanding Official Action, claims 1-5 and 7-10 were rejected by the Examiner pursuant to 35 USC §102(b) as allegedly being anticipated by BRACHER, *The Structure of Neocalliactine Acetate - Proof by Total Synthesis*. The Official Action stated that BRACHER teaches "pentacyclic aromatic compounds according to formula 12 … which are the same as the compounds of instant formula I, wherein R_3 is lower alkoxy … ." This rejection is respectfully traversed.

In imposing the rejection, the Official Action cites to compound 12 of BRACHER. However, compound 12 is a synthetic intermediate for new calliactine acetate. BRACHER does not disclose or suggest a pharmaceutical composition for treating tumors. Indeed, BRACHER fails to teach a composition in combination with pharmaceutically acceptable salts and acids. Moreover, compound 12 is isolated from organic layers which are not suitable for pharmaceutical composition. As a result, BRACHER does not anticipate claims 1-5 or 7-10.

Claims 1-5, 7-10, and 12 additionally were rejected pursuant to 35 USC §103(a), as being unpatentable over SCHMITZ et

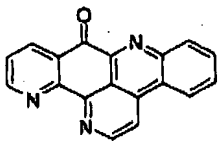
al. and BRACHER.

The Official Action alleged that SCHMITZ et al. teach biologically active polycyclic aromatic compounds with cytotoxic activity isolated from marine organisms such as ascididemin (compound 2, page 1395). The Official Action also alleged that BRACHER teach polycyclic aromatic alkaloids derived from marine organisms with cytotoxic and anti-cancer activity (compound 4A, page 59).

In light of those findings, the Official Action concluded that "[t]o those skilled in chemical art, the instant elected group of pentacyclic aromatic alkaloid compound is not such an advance over the genus of compounds previously published in Schmitz *et al.* and Bracher et al. references, as requires invention, because chemists knowing the cytotoxic properties of the known ascididemin compounds would know what to expect in a genus of compounds that overlaps the known compounds." Specifically, the Official Action stated "[n]othing unobvious is seen in substituting the known claimed 2-bromo isomer for the structurally similar 3-bromo isomer, as taught by both Schmitz and Bracher, since such structurally related compounds suggest one another and would be expected to share common properties, absent a showing of unexpected results … ." To support this conclusion, the Official Action cited *in re Norris*, 84 USPQ 458 (1950). This rejection is respectfully traversed.

Indeed, SCHMITZ et al. disclose the cytotoxic activity assessed *in vitro* on a P388 model of the compounds ascididemin

(3), 2-bromoleptoclinidone (2) and of the compound (7) having on the aromatic ring a hydroxy group on position 10.



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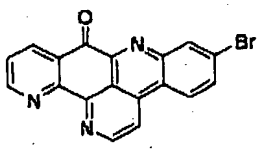

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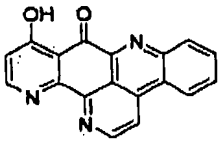
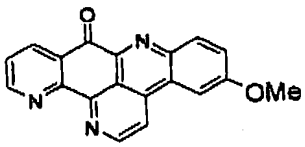


(7)

BRACHER also discloses one compound of Formula (1) substituted in position 5 (compound 12 hereafter):



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However, this compound is disclosed as an intermediate, and the document does not give any information regarding the cytotoxic activity of the compound.

This stands in contrast to the claimed invention. The claimed pharmaceutical composition comprises compounds of formulae (1) and (1a) as set forth in the claimed invention substituted on the ring D on position 5, i.e. wherein R3 is different from H.

Moreover, neither SCHMITZ et al. nor BRACHER disclose nor suggest replacing the hydrogen atom on position 5 on the ring D by the meaning of R3 listed in claim 1. Further, BRACHER does not provide one of ordinary skill in the art any motivation to do

so, as the publication does not give any information regarding the cytotoxic activity of compound (12).

The Examiner's attention is directed to *In re Fitch* (Fed. Circ. 1992) wherein it was held that: "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modifications obvious unless the prior art suggested the desirability of the modification".

Further, it should be highlighted that, in the field of drug design, any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, expected a priori to disturb the pharmacological activity profile of the initial structure.

Indeed, the claimed compounds display both an antitumoral activity and a tolerance/cytotoxicity ratio superior than the compounds cited by the Official Action, which render the compounds suitable for therapeutical use as antitumoral agents.

In fact, the pharmaceutical compositions according to the invention display an *in vitro* tolerance/cytotoxicity (MTD/IC50) ratio superior than those obtained with ascididemin or 2-bromoleptoclinidone, as evidenced by the results in Table III in the present specification.

As an example, compound CRL 8423 displays a MDT/IC 50 ratio 114 times higher than that of ascididemin and 57 times higher than that of 2-bromoleptoclinidone.

In another example, 3-bromoleptoclinidone corresponding to CRL 8248 (Example 8), which is a positional isomer of 2-bromoleptoclinidone, also displays a tolerance value, as well as a tolerance/cytotoxicity (MTD/IC50) ratio (*in vitro*) far higher than 2-bromoleptoclinidone, as reported in Tables I and III of the specification.

This cytotoxic activity associated with a good tolerance of the claimed pharmaceutical composition is believed to be due to the fact that ascididemin derivatives are substituted in position 5 on ring D by the groups listed in claim 1 as amended.

Thus, SCHMITZ et al. and BRACHER do not disclose or suggest any ascididemin derivatives substituted in position 5, and nothing gives incentive to the person skilled in the art to introduce a chemical group on that position of the aromatic ring D in view of obtaining cytotoxic compounds with a better tolerance.

At this time, the Examiner is also reminded that isomerism alone cannot negate patentability in the absence of a relationship of the isomers to each other which would suggest the claimed compounds. *Ex parte Hogg et al.*, 121 USPQ 96 (POBA 1959). Moreover, while position isomerism involves close similarity between compounds, it must be considered along with all other relevant acts in determining the issue of obviousness under 35 U.S.C. § 103. *In re Wiechert*, 370 F.2d 27, 152 USPQ 247 (CCPA 1967). Indeed, a novel useful compound which may be

isomeric with a compound of the prior art is still patentable if, as is the case herein, it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. *In re Norris*, 179 F.2d 970, 84 USPQ 458 (CCPA 1950).

Finally, the Examiner's attention is respectfully directed to the Declaration Under Rule 132 of Françoise COLLIGNON filed herewith in the attached Appendix to this amendment. In that Declaration, Monsieur COLLIGNON explains that experimental data were submitted with results showing that the activity of the compounds claimed by applicants, notably CRL 8248, CRL 8325, CRL 8347, CRL 8406, CRL 8407, CRL 8416, and CRL 8422 are unexpectedly much more superior than the activity of ascididemin. Specifically, the Examiner respectfully is referred to the specification (page 51, lines 7-9), wherein it is disclosed that "all of the compounds show significant inhibitory activity on the cell proliferation of the 12^{th} human tumor lines … ."

Moreover, as noted above, Table III in the present specification illustrates that the compounds show results on the tumor cell line models, IC 50_{IC} values (nM) which are greater than or equivalent to that of ascididemin. The results are considered to be markedly higher than those of ascididemin. Such results suggest that this novel family of compounds has no direct toxicity. Consequently, the tolerance/cycotoxic activity ratios of the compounds in the present invention are markedly higher than that of the natural ascididemin.

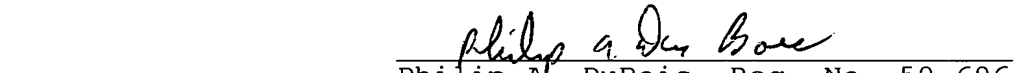
These compounds thus may be used as antitumor drugs, for the cycotoxic properties, at tissue concentrations that are higher than those induced with the natural ascididemin. They similarly are characterized by a far better therapeutic manageability. As such, it respectfully is submitted that BRACHER et al. and SCHMITZ et al. fail to anticipate or render obvious the claimed invention.

In view of the present amendment and the foregoing remarks, therefore, it is believed that the present application now is in condition for allowance. Passage to issue on that basis accordingly respectfully is requested.

The Commissioner hereby is authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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APPENDIX:

The Appendix includes the following item:

- a 37 CFR 1.132 Declaration